is shown against pathogenic forms. Weaker solutions while not so strongly amebacidal, exercise a definitely deleterious action on the parasite. To obtain a 1 to 100,000 solution in the blood it would be necessary to have about 0.05 gm. of emetin in the circulation at one time. As the dose given is generally smaller than this, and it is not completely taken up into the blood stream from the point of injection for some hours, it is evident that the dilution is considerably greater than this figure. It seems safe to assume, however, that emetin is excreted along the whole alimentary tract. In this case its longer stay in the excretory tissues, or the greater concentration in which it may exist during excretion, would account for a sufficiently strong amebacidal action.

Contrary to the statement of Lowin we have found, on patients, that emetin usually produces a definite local irritation after a subcutaneous or intramuscular injection. There is some redness, pain, swelling and occasionally edema in the part, most marked for the first two or three days, and gradually subsiding in about a week. If applied to mucous membranes there appear small pin-head-sized vesicles which rupture, leaving small ulcers. These, however, rapidly disappear. These effects are undoubtedly well known to all who have been using emetin in the treatment of pyorrhea alveolaris.

SUMMARY. From our experiments we wish to emphasize the following points:

1. Emetin depresses and may eventually paralyze the heart.
2. It is a powerful gastro-intestinal irritant whether given by mouth or subcutaneous injection.
3. It causes a definite derangement of metabolism, characterized by an increase in nitrogen loss and an acidosis.
4. While in normal individuals given moderate doses, these actions may not be of importance, in pathological states of the circulation, intestinal tract, or metabolism, they may be a very definite source of danger.

EFFECTS OF RETENTION IN THE KIDNEY OF MEDIA EMPLOYED IN PYELOGRAPHY.

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WITH the recognition of the diagnostic value of pyelography came the realization that the method was not without danger to the patient. Deaths were reported by various observers, which

were evidently the direct result of pyelography. Animal experimentation demonstrated that death might follow the introduction of colloidal silver solution into the renal pelvis with overdistention. The introduction of the medium by means of gravity so as to obviate the danger of overdistention reduced the possibility of renal injury to a great degree.

In 1913 one of us[1] reported several cases of hydronephrosis removed at operation in which necrosis of the renal cortex was evident, although the pelvis had not been overdistended. It was believed that secondary retention of colloidal silver in the renal pelvis without overdistention could cause necrosis in the renal parenchyma. This observation was later corroborated by Krotoszyner[2] and by Keyes and Mohan,[3] who reported similar clinical observations. Keyes and Mohan further demonstrated the process conclusively by injecting a small amount of colloidal silver into the renal pelvis of dogs and then ligating the ureter. The kidneys removed later showed numerous areas of cortical necrosis as the result of the retention of the colloidal silver. From a histological study of the areas of resulting necrosis it was evident that the minute particles of metallic silver deposited in the parenchyma were the underlying cause of the necrosis.

The avenues of introduction of the metallic deposits have not been definitely determined. It has been argued that the silver deposits found in the tubules reached the glomeruli primarily by means of lymphatic and vascular absorption, and were later secreted into the tubules. The histological evidence advanced in support of this theory is hardly conclusive. It would seem logical to hold that when the natural drainage of the renal pelvis is occluded, peristaltic contraction may force the pelvic contents into the tubules. Microscopic examination of any of the different solutions of colloidal silver employed in pyelography will show the presence of undissolved particles of metallic silver; a perfect solution is hardly possible, a fine suspension being the medium employed. The silver deposited in the renal substance acts like any other foreign body in that it causes suppuration and necrosis of the adjacent tissue. With multiple deposits of metallic silver with adjacent foci of infection the resulting condition is practically that of an acute septic nephritis. As might be expected, clinical symptoms and resulting fatality are identical with acute septic nephritis. Necessarily, the indications for surgical treatment are similar in both conditions. Nephrectomy is indicated if the patient has a

[1] Braasch, W. F.: Recent Progress in Ureteropyelography. Jour. Michigan Med. Soc., 1913, xii, 189–190.

[2] Krotoszyner: Untoward Results of Pyelography. Surg., Gynec. and Obst., 1914, xix, 522–527.

[3] Keyes, E. L., and Mohan, H.: The Damage Done by Pyelography. Am. Jour. Med. Sc., 1915, cxlix, 30–41.

persistent high temperature and evidence of severe intoxication, which usually marks this condition following pyelography. That such a complication will occur in a comparatively small percentage of cases of hydronephrosis following pyelography made with proper technical precaution is evidenced by the fact that in more than 5000 cases at the Mayo Clinic in which pyelography was employed, marked focal necrosis was found in but eight cases. In all of these the kidney was found to be actively secreting, although the drainage was temporarily interfered with. Less reaction followed when the substance of the kidney was largely destroyed. No deaths occurred which could be attributed directly to pyelography. However, the element of danger which is present in spite of every precaution would necessarily restrict its employment.

To prevent pyelography from falling into disuse as a method of diagnosis because of the possible danger involved in its employment, various forms of silver have been tried. Among the different media suggested, silver iodide in emulsion[4] and silver iodide in suspension[5] have been found less harmful in their effect. Although the frequency of focal necrosis was thus unquestionably diminished, nevertheless it was not entirely eliminated. Two severe cases of focal necrosis following the retention of silver iodide injected into a hydronephrosis came under our observation. Moreover, the silver iodide suspension causes considerable local irritation. The injection of so viscid a substance as silver iodide emulsion with a syringe is objectionable because of the difficulty of gauging the degree of pressure in its introduction and the amount necessary for pelvic distention. The latest medium suggested, namely, thorium,[6] evidently obviate many of the objections to those previously used, and has the following advantages: (1) it is in actual solution and not suspension; (2) it does not cause local irritation; (3) it can be introduced by means of gravity.

Thorium nitrate solution offers the safest medium for pyelography. Unfortunately, it casts a less distinct shadow than the colloidal silver preparations in common use. Further, it does not bring out the details of the calyces nor of the ureter as well as the silver preparation. It is peculiar that solutions of greater concentration (20 per cent.) cast no denser shadow than a lesser (10 or 15 per cent.).

That focal necrosis may occasionally occur following the use of thorium was evident in a case of hydronephrosis which recently came under our observation. Microscopic examination of the

[4] Kelly, H. A., and Lewis, R. M.: Silver Iodide Emulsion—a New Medium for Skiagraphy of the Urinary Tract. Surg., Gynec. and Obst., 1913, xvi, 707–708.

[5] Young, E. L.: A New Preparation for Pyelography. Boston Med. and Surg. Jour., 1915, clxxii, 539–544.

[6] Burns, J. E.: Thorium, a New Agent for Pyelography. Preliminary Report. Jour. Am. Med. Assn., 1915, lxiv, 2126–2127.

tissue of the kidney removed showed numerous areas of round-celled infiltration such as are usually the result of infection. No evidence of metallic deposit was visible. The infection was predominant in the tissues, about the tubules and but few glomeruli were involved.

Prior to the use of pyelography the diagnosis of renal urinary retention was usually arrived at by means of the ureteral catheter and the overdistention method. Following simple ureteral catheterization we have observed the presence of a considerable degree of focal suppuration in several kidneys subsequently removed at operation. Microscopic examination of these areas showed that they were of bacterial origin. It is quite impossible to introduce either a ureteral catheter or bland fluid into the renal pelvis which has insufficient drainage without danger of subsequent infection. However, the exercise of every precaution to keep such a catheter and the medium introduced sterile will somewhat reduce the number of cases of infection, but will not exclude them. We are under the impression that the focal necrosis and areas of suppuration noted in the case with thorium retention were the result of coincident bacterial infection. The use of opaque media, as in pyelography, should not bear the entire blame for cortical necrosis. Moreover, the kidney in which focal necrosis results following retention is primarily a "surgical kidney," and its sacrifice will not usually alter the necessary procedure. As a matter of precaution it is advisable always to ascertain whether the other kidney is functionating properly before either catheterization, fluid overdistention, or pyelography is attempted in a case in which pelvic retention is suspected.

The object of the following series of experiments which were begun in April, 1914, was to study the comparative effect of retention in the kidney of the various media used in pyelography and to determine whether the retention of chemical irritants in the pelvis of the kidney would produce lesions of that organ. This was accomplished by either a complete or partial occlusion of the ureter of a dog after injecting the substance into the pelvis of the kidney. The routine technic was to expose the ureter, usually the right, through a lumbar incision and carefully dissect it free for a short distance, about two inches, from the kidney. When the occlusion was made complete the free portion of the ureter was ligated and the solution injected through it into the pelvis. The ureter was again ligated proximal to the entrance of the needle and sectioned between the ligatures. When a partial occlusion only was made the ligature was tightened over the needle at the point where it entered the lumen of the ureter. As the results did not materially differ, all the experiments will be reported together.

The capacity of the dog's kidney varies, but is practically always greater than 1.5 c.c. In order to avoid immediate distention of the pelvis, only 1 c.c. was used. After injecting and ligating the ureter

it was replaced and the wound carefully closed. The specimens were obtained at various times after injection, but were approximately the same for the different substances used.

The effects of retention of the following substances were studied experimentally: (1) 1 per cent. solution sodium chloride; (2) saturated solution of boracic acid; (3) saturated solution of sodium citrate; (4) methylene blue; (5) 5 per cent. collargol; (6) 25 per cent. collargol; (7) 25 per cent. argyrol; (8) 25 per cent. cargentos; (9) washed staphylococci; (10) emulsion of silver iodide; (11) silver iodide in quince-seed emulsion; (12) 15 per cent. thorium nitrate neutralized; (13) 20 per cent. solution of thorium nitrate as used clinically; (14) 20 per cent. solution of thorium nitrate unneutralized. In many of these experiments the uninjected kidney was also studied.

In studying the kidney it was necessary to differentiate three distinct conditions: (1) the effect of the hydronephrosis; (2) the effect of the infection; (3) the effect of the retained substances. The effect of the hydronephrosis on the substance of the kidney could easily be distinguished. However, it was not always possible to determine whether the condition found in the kidney was due to an infection, to the retained substance, or to both.

Grossly, the kidney usually presented a degree of hydronephrosis depending on the length of time after ligation. The fluid which escaped from the pelvis was quite often very turbid, and it was often possible to find some of the injected solution. In a few cases there was a necrosis of the ureter at the point of ligation, with the formation of a perinephritic cyst.

The capsule was usually thickened. On section the renal substance was thin and firm. Quite often it was not possible to demonstrate grossly any changes in the substance of the kidney due to the injected solution. However, in some instances there were pin-point hemorrhagic areas or small abscesses. These were usually in the cortex near the surface. In two instances the medulla was stained throughout with the injected substance. The pelvic mucosa practically always showed changes. These consisted of hemorrhagic spots or areas of necrosis. The mucosa was usually stained with injected solution, and some of the substance could be scraped from the surface. The result of the microscopic study is as follows:

No.	Solution.	Time.	Change.
1	Methylene blue	10 days	None.
2	" "	26 "	Slight. A few areas show infiltration.
3	" "	15 "	None.
4	" "	22 "	None.
5	" "	12 "	Moderate. Several areas of focal inflammation. Infection?
6	5 per cent. collargol	15 "	Marked. Entire medulla infiltrated; areas of necrosis; several cortical areas of pigmentation.

No.	Solution.	Time.	Change.
7	5 per cent. collargol	9 days	Moderate. Several areas of infiltration of deeply staining cells.
8	" " "	25 "	Marked. Many areas of pigmentation definitely organized throughout the remaining renal substance.
9	" " "	15 "	Slight. A few areas of infiltration.
10	" " "	8 "	Moderate. Several areas of necrosis.
11	" " "	7 "	None.
12	" " "	14 "	Slight. Several areas of infiltration of deeply pigmented cells in the cortex.
13	25 per cent. collargol	25 "	Marked. Entire remaining renal substance infiltrated. Few normal cells left. Many areas of necrosis.
14	" " "	30 min.	Very slight.
15	" " "	7 days	Slight. Many cells of the collecting tubules pigmented.
16	20 per cent. collargol	7 "	Slight infiltration of the pelvic mucosa.
17	25 per cent. collargol	4 "	None.
18	25 per cent. argyrol	22 "	Marked. Infiltration of all the remaining renal substance.
19	" " "	5 "	None.
20	" " "	24 "	Moderate. Marked infiltration with several areas of necrosis.
21	" " "	15 "	Slight. A few areas of pigmentation.
22	" " "	8 "	Very slight.
23	" " "	7 "	None.
24	25 per cent. cargentos	30 "	Marked. Many areas of pigmentation scattered throughout the remaining renal substances.
25	" " "	13 "	Moderate. Many areas of pigmentation found mainly in the medulla.
26	" " "	30 "	Marked. Remaining renal substance infiltrated. Many areas of necrosis.
27	" " "	5 "	Slight. Several collecting tubules contain the brown-colored substance. Pelvic mucosa is infiltrated.
28	" " "	7 "	Slight. A very few areas infiltrated with deeply staining cells.
29	" " "	7 "	None.
30	Silver iodide	24 "	None.
31	" "	15 "	None.
32	" "	16 "	Moderate. Marked infiltration.
33	" "	7 "	None.
34	" "	12 "	Very slight.
35	Emulsion silver iodide with quince seed	7 "	Very slight.
36	Emulsion silver iodide with quince seed	7 "	Very slight.
37	Emulsion silver iodide with quince seed	9 "	None.
38	Emulsion silver iodide with quince seed	58 "	No renal structure left.
39	Emulsion silver iodide with quince seed	9 "	None.
40	Washed staphylococci	3 "	Slight. A few abscesses.
41	" "	2 "	Marked. Many abscesses.
42	" "	5 "	Moderate. A few abscesses.
43	15 per cent. thorium nitrate	4 "	None.
44	15 per cent. thorium nitrate	9 "	None.
45	15 per cent. thorium nitrate	14 "	None.

No.	Solution.	Time.	Change.
46	15 per cent. thorium nitrate	6 days	None.
47	15 per cent. thorium nitrate	10 "	Slight?
48	1 per cent. NaCl	4 "	None.
49	" "	10 "	None.
50	Saturated solution, boracic acid	10 "	None.
51	Saturated solution, boracic acid	6 "	None.
52	20 per cent. solution thorium nitrate	10 "	Microscopic picture: Acute infection. Renal substance filtrated throughout, complete loss of normal structure in many areas. Definite abscesses in some areas.
53	20 per cent. solution thorium nitrate	6 "	Marked. Substance of kidney infiltrated throughout. Definite abscesses in some areas. Tubule mostly disappeared or badly damaged. Glomeruli seem less affected than tubules.
54	20 per cent. solution thorium nitrate	7 "	None.
55	20 per cent. solution thorium nitrate	4 "	Slight.
56	Saturated solution citrate	7 "	A few small subcortical infiltrations which appear to be beginning abscesses.
57	Saturated solution citrate	4 "	None.
58	20 per cent. solution thorium nitrate	3 "	None.
59	20 per cent. solution thorium nitrate	3 "	None.
60	Saturated solution citrate	3 "	Slight. There are a few areas of beginning infiltration.
61	20 per cent. solution thorium nitrate	3 "	Slight. There are a few areas of beginning infiltration.
62	20 per cent. solution thorium nitrate	7 "	None.
63	20 per cent. solution thorium nitrate	7 "	Slight. There are a few beginning areas of infiltration.
64	20 per cent. solution thorium nitrate	3 "	Moderate. There are a few very large areas of infiltration in the cortex.
65	Saturated solution citrate	7 "	None.
66	20 per cent. solution thorium nitrate (unneutralized)	2 "	Moderate. There are some cortical areas of infiltration.
67	20 per cent. solution thorium nitrate (unneutralized)	2 "	Moderate. There are a few areas of beginning infiltration.

An attempt was made to estimate the changes due to the injected solution. These changes varied, but in general they consisted of areas of focal necrosis with or without actual demonstration of the localized substance. These areas were usually located in the cortex but have been found in the medulla. The lesion appears to consist of an accumulation of the substance in the tubules of the kidney. We have not definitely determined whether the sub-

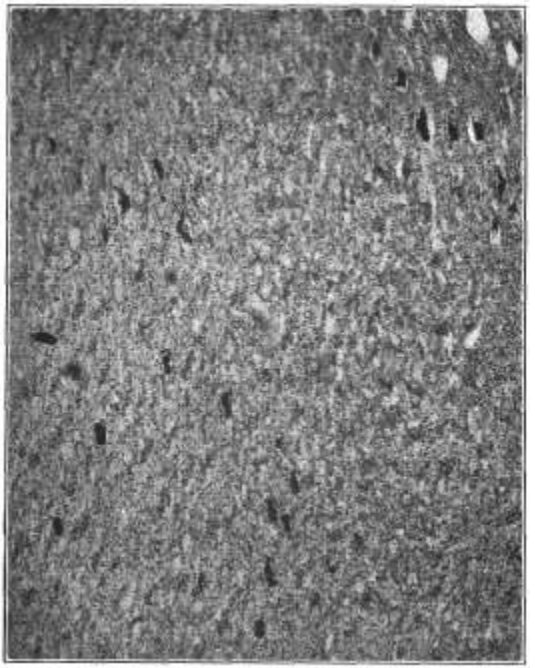

FIG. 1.—Experiment 27. Photomicrograph (× 50) showing cargentos in kidney tubules five days after injection.

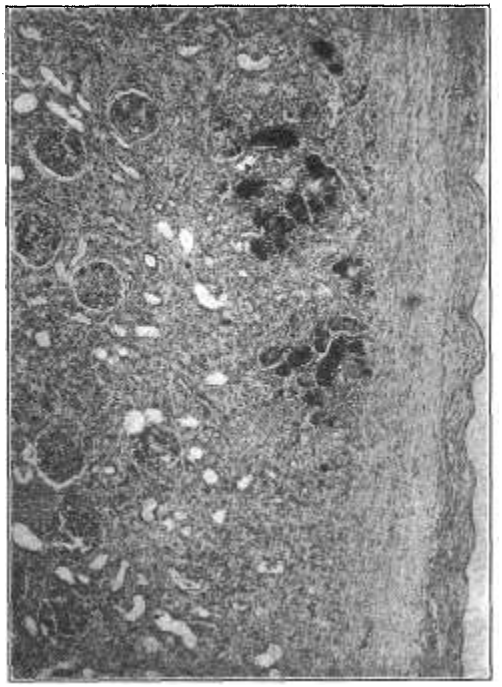

FIG. 2.—Experiment 6. Photomicrograph (× 60) showing collargol in the kidney tubules fifteen days after injection.

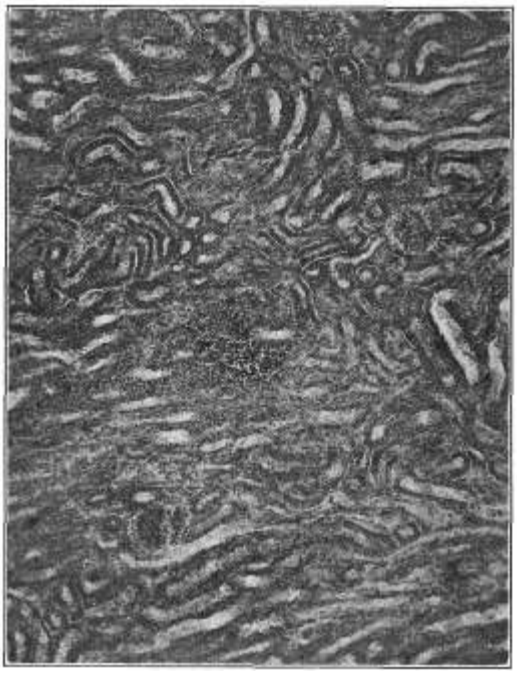

FIG. 3.—Experiment 25. Photomicrograph (× 60) showing a localized area of cargentos thirty days after injection.

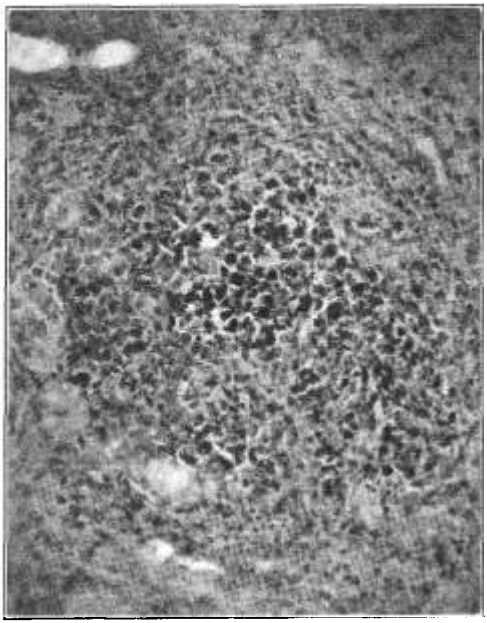

FIG. 4.—Experiment 8. Photomicrograph (× 200) showing a higher magnification of one of the areas in Fig. 3.

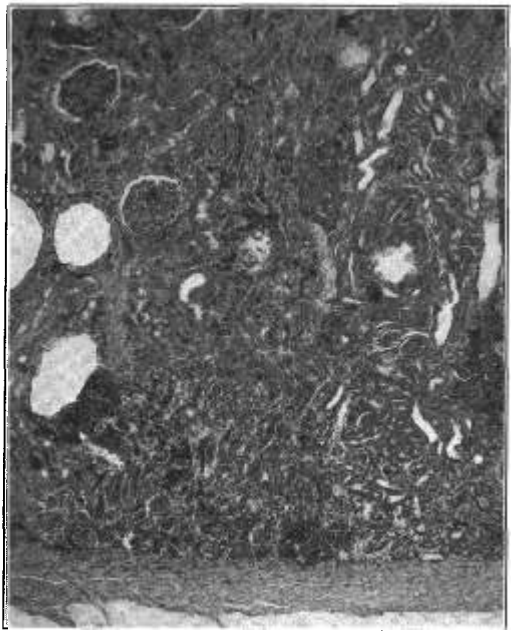

FIG. 5.—Experiment 47. Photomicrograph (× 50) showing some areas of infiltration in the periphery of cortex ten days after the injection of thorium nitrate.

FIG. 6.—Experiment 47. Photomicrograph (× 225) showing higher magnification of one of the areas in Fig. 5. It is impossible to tell what part the solution played in its formation. It appears to be primary infection.

stance reaches the cortex through the tubules or by way of the blood and lymphatic vessels. Observations tend to show that in some instances either route may be followed. In a few instances lesions of the uninjected kidney have proved that the substance was absorbed and excreted. The lesions which follow excretion of the substance are usually located in the medulla. These are characterized by infiltration of large deeply staining cells. When organization takes place there is first formed an area of necrosis and hemorrhages in the immediate vicinity of the substance. Later a definite wall of connective tissue forms with absorption of the necrotic material. In many instances infection followed the localization of the substance so that it was impossible to differentiate the condition from a primary infection.

RESULTS. The results of these experiments are tabulated briefly as follows:

1. The injection of 1 per cent. solution of sodium chloride and a saturated solution of boracic acid in two experiments each did not produce a lesion of the kidney.

2. The injection of a saturated solution of sodium citrate in four experiments produced lesions in two instances. The cultures of tissue was negative for bacteria in both of these positive experiments, and in one only were a few micrococci found in the fluid of the pelvis.

3. In the five experiments in which methylene blue was injected only one kidney showed a slight lesion. This lesion may have been due to an infection.

4. In seven experiments 5 per cent. collargol was injected. Lesions of various degrees of severity occurred in six.

5. In the five experiments in which 25 per cent. collargol was injected, lesions were found in four.

6. The injection of 25 per cent. arygol in six experiments produced lesions in four.

7. The injection of 25 per cent. cargentos in six experiments produced lesions in four.

8. In five experiments in which silver iodide was injected, moderate lesions were noted in two.

9. In five experiments in which silver iodide with quince seed was injected, slight lesions were found in two.

10. In five experiments 15 per cent. thorium nitrate was injected. A slight lesion was noted in one kidney. In order to test this substance to a greater extent, in one experiment the pelvis of the kidney was overdistended with 5 c.c. of the solution and in another 2.5 c.c. were injected. The first specimen was examined after four days and the latter after fifteen days. In neither were any changes noted which could be attributed to the injected solution.

11. The injection of a 20 per cent. solution of thorium nitrate, neutralized as used clinically, in ten experiments, produced lesions

of various degrees of severity in five. In two of these the kidney was very badly damaged. It is suggestive that in these two experiments the solution was used immediately after it had been made. It is possible that an old solution is better than one just freshly prepared. In the other three experiments in which lesions occurred the cultures of tissue and smears of the pelvic fluid were negative for bacteria.

12. The injection of 20 per cent. solution of thorium nitrate, unneutralized, in two experiments, produced lesions, particularly of the pelvis, in both. Smears of the pelvic fluid were negative in both of these experiments and cultures of tissue showed a few staphylococci, possibly a contamination.

CONCLUSIONS DERIVED FROM CLINICAL DATA. 1. The greatest danger in the use of silver preparations is their retention in actively secreting kidneys.

2. With multiple foci of necrosis the condition should be regarded as a septic nephritis and immediate nephrectomy is indicated.

3. Focal necrosis as the result of infection may follow the introduction of a ureteral catheter or of bland fluids into a pelvis with insufficient drainage.

4. Silver iodide suspensions are less harmful than the colloidal silver preparations.

5. Thorium nitrate in 10 or 15 per cent. solutions causes the least reaction but casts a less distinct shadow.

CONCLUSIONS DERIVED FROM EXPERIMENTAL DATA. 1. Mild chemical irritants, as sodium chloride and boracic acid, when injected and retained in the pelvis of the kidney do not produce lesions of that organ.

2. The effect of methylene blue was practically negligible.

3. More stringent chemical irritants, as sodium citrate and 20 per cent. thorium nitrate, when tested in the same drastic manner, produce lesions of the kidney, which seem directly due to the chemical injected, and not to any concomitant or subsequent infection.

4. Argyrol, collargol, and cargentos were about equally responsible for producing the most marked changes noted. It was often possible to find areas in which the metal could be distinguished.

5. The weaker solutions of colloidal silver did not appear to be less harmful than a more concentrated solution.

6. The silver iodide preparations produced less changes in the kidney than the other silver solutions. Of the two preparations of silver iodide, the one in which it is suspended in quince-seed emulsion caused the least necrosis.

7. So far as we have been able to determine by the method employed, thorium nitrate (15 per cent. solution) did not produce changes in the kidney except possibly in one experiment. Care must be taken in its preparation that the solution is thoroughly neutralized.